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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,020	12/31/2001	Yuehua Li	5051-451IP	8515

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,020	LI ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The rejection of claims 1, 6-11, 14-19, 24-25, 39, 42-43, 48, 50, and 67-76 under 35 U.S.C. 112, first paragraph, is withdrawn in response to Applicant's cancellation of these claims. However, Applicant's arguments and the submission of the Parikh Declaration will be addressed in regards to the rejection of the newly added claims set forth below.

2. Applicant's arguments with respect to claims 1, 6-11, 14-19, 24-25, 39, 42-43, 48, 50, and 67-76 have been considered but are moot in view of the new ground(s) of rejection.

Response to Amendment

3. The Parikh Declaration under 37 CFR 1.132 filed 9-06-2005 is insufficient to overcome the rejection of claims 77-110 based upon 35 U.S.C. 112, first paragraph, set forth below because: The data provided in the Parikh Declaration is not commensurate in scope with the breadth of the instantly claimed invention. For example, there is no clear demarcation (i.e. no upper limit) for the N-terminal sequence, and since the claims recite from about 10 to about 50 contiguous amino acids *from* the N-terminal sequence, it is not necessary for the claims to be limited to only those contiguous peptides that comprise at least about amino acids 1-10 of SEQ ID NO: 3. The scope of peptides selected *from* the N-terminal sequence therefore encompasses peptides that do not necessarily include the first 10 or even the first 24 amino acids of SEQ ID NO: 3. Moreover, with the exception of claims 83-84, and 90 the instant claims do not require that the peptides be myristoylated.

Furthermore, it is noted that after treatment of the animals in Applicant's experiments, the animals then were sacrificed in order to determine the level of mucus secretion in a mouse model of asthma. However, there is no evidence that the observed reduction in mucus secretion actually correlated into the amelioration of the symptoms of asthma, since the state of the art, see Barnes (2002) and Rogers (2001 and 2003) as described below, calls into question the actual clinical benefit of mucus inhibitory agents for the treatment of respiratory diseases with associated mucus hypersecretion.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 77-110 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description/New Matter).

Claims 77-94 are generically drawn to the methods or formulations comprising a peptide consisting of from about 10 to about 50 contiguous amino acids from the N-terminal sequence of SEQ ID NO: 3, wherein said peptide inhibits MARCKS protein-related mucous hypersecretion, however the specification as filed defines only one

peptide that demonstrates the ability to inhibit MARCKS related mucous hypersecretion, that is the MANS peptide (myristic acid-SEQ ID NO: 1)

The instant claim language appears to encompass subsequences of the N-terminal sequence of SEQ ID NO: 3, specifically peptides consisting of from about 10 to about 50 contiguous amino acids ***from*** the N-terminal sequence of SEQ ID NO: 3. The instant claims do not require the full length sequence set forth in SEQ ID NO: 3 or 1; but rather encompasses any amino acid sequence comprising *any subsequence of SEQ ID NO: 1or 3 that is from about 10 amino acids in length.* However, the specification does not appear to have provided sufficient guidance, other than the specific sequence of SEQ ID NO: 1, as to which subsequences of SEQ ID NO: 1 or 3 would share the function of inhibiting mucin secretion dependent signaling. Neither does the specification appear to have provided any working examples of any functional subsequences. Thus it would require further experimentation of the skilled artisan to determine which subsequences of SEQ ID NO: 1 would have the function of the full-length molecule. Applicant's submission of the Parikh Declaration, providing additional experimental data regarding the ability of peptides BIO-120, BIO-116, BIO-112, BIO-110 is evidence that further experimentation was required to identify the full scope of compounds encompassed by the instant claims. It is clear that the myristolated sequences of BIO-120, BIO-116, BIO-112, and BIO-110 all share at least the first 10 contiguous amino acids of SEQ ID NO: 1 and 3, however there is no specific guidance in the specification as filed, that would have lead the skilled artisan to the specific structures of BIO-120, BIO-116, BIO-112, and BIO-110 apart from further

experimentation, as set forth in the Parikh Declaration. There was no support in the specification as originally filed for the specific structures of these compounds, because they were empirically determined. Furthermore, as stated above, the instant claims are not limited to only those peptides that necessarily include the first 10 contiguous amino acid from SEQ ID NO: 3, since the scope of the claims encompass peptides that are subsequences of the N-terminal sequence of SEQ ID NO: 3.

Claims 100, 106, and 110 recite wherein said MANS peptide consists of a peptide of SEQ ID NO: 1 or a myristolated peptide of SEQ ID NO: 1. There is no support for this limitation in the specification as filed, according to the specification at page 21, last paragraph, "[A] myristoylated polypeptide, 24 amino acids in length, with sequence Myristic-acid-GAQFSKTAAKGEAAAERPGEAAVA (SEQ ID NO: 1), is referred to herein as the MANS peptide for myristolated N-terminal sequence." Therefore the recitation wherein the MANS peptide is selected from SEQ ID NO: 1 or a myristolated peptide of SEQ ID NO: 1 is improper, and there is no such support for this limitation in the claims.

6. Claims 77-110 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting mucus secretion *in vitro,* and for decreasing mucus secretion in a mouse model of asthma comprising the administration of the MANS-peptide, does not reasonably provide enablement for the *in vivo* therapeutic treatment of bronchitis, cystic fibrosis, chronic obstructive pulmonary disease comprising inhibiting mucus secretion by the administration of any other peptide consisting from about 10 to about 50 contiguous amino acids from the N-terminal

sequence of SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to us the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The scope of the claimed methods encompass the *in vivo* treatment of any disease associated with hypersecretion of mucous, dependent claims are also limited to

the treatment of a subject that suffers from a disease or condition in which airway mucus hypersecretion is a dominant clinical finding, such as bronchitis, asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD), bronchiectasis, emphysema, pneumonia, influenza, rhinitis, and the common cold. However, the claims are limited to the administration of peptides that inhibit only MARCKS protein-related mucous hypersecretion.

The instant claim language appears to encompass subsequences. The instant claims do not require that the full length sequence set forth in SEQ ID NO: 3 or 1; but rather encompasses any amino acid sequence comprising either the full length of SEQ ID NO:1 or *any subsequence that is from about 10 amino acids in length.*. However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO:1 would share the function of inhibiting mucin secretion dependent signaling. Neither does the specification appear to have provided any working examples of any functional subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO: 1 would have the function of the full-length molecule.

According to Rogers (2003), current treatments of diseases associated with airway mucus hypersecretion, such as cystic fibrosis, asthma, and bronchitis (see instant claims 88 and 103) do not take into account the homeostatic role of pulmonary mucus, and the impact of mucus on respiratory pathophysiology. According to Rogers (2003) optimal treatment should aim at the reversion to normal levels of secretion, rather than merely to inhibit hypersecretion (see page 178).

Additionally, Rogers (2001) states:

"Although not diagnostic for the condition, mucus hypersecretion clearly contributes to morbidity and mortality in certain groups of patients with COPD. This suggests that it is important to develop drugs that inhibit mucus hypersecretion in these patients, although without affecting normal mucus secretion and mucociliary clearance. Before these questions can be addressed, considerably more needs to be known about the biochemical and biophysical nature of airway mucins in normal healthy subjects, as well as which mucin gene products predominate. Following on from this, investigations need to be directed at determining whether or not there is an intrinsic abnormality in mucus in COPD, and whether any abnormality is specific for COPD compared with other hypersecretory conditions of the airways such as asthma. The factors which regulate MUC gene expression in health and disease, and the relationship between this regulation and the development of the hypersecretory state, will also need to be determined. The above data can then be used in deciding therapeutic targets leading to rational design of antihypersecretory drugs for COPD."

The instant claims are directed to methods of inhibiting mucus secretion *in vivo,* wherein the scope of the invention encompasses the therapeutic treatment of diseases associated with hypersecretion, however, there is no direct correlation between the *in vitro* inhibition of MARCKS protein and the production of treatment effects for diseases *associated* with mucus hypersecretion. Furthermore, there is no guidance for inhibiting mucus hypersecretion, while maintaining the normal levels of mucus in a patient, there is no specific guidance in this regard.

There is no evidence of record that demonstrates that the MANS peptide would function to modulate those inflammatory mediators. The lack of any working examples is exacerbated because the invention is in a highly unpredictable art-regulating the airway mucus hypersecretion-and while the level of skill of a practitioner in the art may be high, the state of the art at the time of the instant invention was that it is in fact unknown and untested what are the underlying inflammatory mediators and the physiologic bases of the therapeutic effects of MANS peptide in the treatment of the inflammation normally associated with airway disorders such as bronchitis, asthma, cystic fibrosis, COPD, etc.

Also, at issue is whether or not the claimed MANS peptide would function to regulate "respiratory disease" including "chronic bronchitis". The specification discloses the inhibition of mucin secretion dependent signaling of PKC/PKG using MANS peptide of SEQ ID NO: 1. The exemplification in the specification is drawn to the blocking of mucin secretion from NHBE cells, a human bronchial epithelial, using *in vitro* ELISA assays. While such *in vitro* assay may provide an indication that particular compounds/compositions are appropriate to target for *further experimental consideration*. Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to extrapolate data obtained from *in vitro* assay to the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention.

The inhibition of mucin secretion of NHBE cells exposed to the MANS peptide of SEQ ID NO: 1, is primarily an in vitro method to assess the suppression of mucin secretion using MANS peptide of SEQ ID NO:1, which is evaluated for use in respiratory diseases therapy. It is unclear which patients would be candidates for in vivo treatment with MANS peptide and when a patient would be given antibiotics, antiviral compounds, antiparasitic compounds, anti-inflammatory compounds or immunosuppressants. In addition, although SEQ ID NO:1 was to block mucin hypersecretion induced by PMA+8-Br-cGMP or UTP of the NHBE cells, it is unclear if these assay results are predictive of a method of regulating an inflammation/cellular secretory process/exocytoic secretion of airway mucin granules/mucus secretion in a subject comprising administering MANS peptide.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since no animals were used as model system to regulate/reduce/inhibit a chronic bronchitis disease or to regulate cellular secretory process. It is not clear that reliance on the *in vitro* data of NHBE cells blocking of mucin secretion accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively regulate a chronic bronchitis disease or cellular secretory process or reach any therapeutic endpoint in mammals by administrating the therapeutic composition of MANS peptide. The specification does not teach how to extrapolate data obtained from an in vitro assay studies to the development of effective in vivo mammalian therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the therapeutic package exemplified in the specification.

In addition, for one to successfully use SEQ ID NO: 1 in vivo, which is suggested to work by blocking PKC/PKG activation (see specification paragraph 65), it is essential to understand if those molecules targeted, actually participate in the pathophysiology of those conditions in vivo, what blocking intervention is most appropriate and the general criteria which will define quantitative endpoints for accessing efficacy (see Ward et al., page 166, section on "Strategies..", in particular). While the specification relies upon inhibiting mucin secretion with SEQ ID NO: 1 as an assay for MANS peptide activity (see paragraph 71 of the instant specification), there is no correlation between merely inhibiting mucous secretion and the *in vivo* production of therapeutic effects in patients

suffering from diseases or conditions such as bronchitis, asthma, cystic fibrosis, chronic obstructive pulmonary disease, bronchiectasis, emphysema, pneumonia, influenza, rhinitis, and the common cold. Barnes (Novartis Found Symp. 248:237-49; discussion 249-53, 277-82, 2002) discusses the current and future therapies for airway mucus hypersecretion. Barnes teaches that several novel targets involved in mucus hypersecretion have recently been identified, including epidermal growth factor receptors, MARCKs, Ca2+-activated Cl- channels and mitogen-activated protein kinases. However, the clinical benefits from inhibiting mucus hypersecretion are still not certain, casting some doubts on this therapeutic approach (see abstract page 237 in particular).

In the Parikh Declaration, submitted by Applicants, the MANS peptide, as well as other peptides containing at least the first 10 amino acids of SEQ ID NO: 1 demonstrated a mucus inhibitory effect in a mouse model of asthma. However, there was not support in the specification as filed for the specific use of the peptides described in the declaration other than the MANS and the RNS peptide. Moreover, Applicants demonstrate a reduction in mucus secretion in the treated mice after the animals were sacrificed, however there is no clear evidence that Applicant's results truly translate into the amelioration of asthma (*or any other respiratory disease associated with mucus secretion*) in the treated animals. As stated above, and as taught in post-filing reviews Barnes (2002, as described above), and Rogers (2001; see page 75), there is controversy concerning the clinical significance and benefit of drugs affecting mucus properties, without addressing the protective benefits of normal mucus secretion

and mucociliary clearance (see also Rogers 2003; page 178, introduction). Therefore, although Applicants demonstrate a reduction in mucus secretion, there is no evidence of the efficacy of the peptides in the treatment of asthma, or any other respiratory disorder associated with mucus hypersecretion.

In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the methods as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed methods with a reasonable expectation of success.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 77-90, and 95-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. The instant claims recited "a method of inhibiting mucus secretion" in the preamble, and further recites "whereby mucus hypersecretion," is reduced. The claims are unclear since the overall methods conclude wherein hypersecretion is reduced, however the preamble merely recites wherein mucus secretion is reduced. The claims are further unclear since it is unclear if the mucus secreting cells or airways treated in the preamble of these methods are in the state of hypersecretion.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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